PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2004/000898	27.09.2004	02.10.2003

International Patent Classification (IPC) or both national classification and IPC
G01N33/68, C12N15/11, C07K14/195

Applicant
RAMOT AT TEL AVIV UNIVERSITY LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Giry, M Telephone No. +49 89 2399-7328

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2004/000898

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 8-19

because:

☒ the said international application, or the said claims Nos. 8-19 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 20-23 and 25-28 (all in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2004/000898

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-28,31-33
	No:	Claims	29-30
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	1-7,20-33
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The search for the subject-matter of claims 20-23 and 25-28 has been carried out insofar as said claims are restricted to the specific embodiments defined in claim 24, *i.e.*, peptides identified by SEQ ID Nos:7-9 (see below Item VIII-1). Consequently, examination of the subject-matter of claims 20-23 and 25-28 with regards to novelty, inventive step and industrial applicability was carried out according to this restriction since claims, or parts of claims, relating to inventions in respect of which no International Search Report has been established need not to be the subject of an international preliminary examination (Rule 66.1(e) PCT).

2. Claims 8-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 - **Reference** is made to the following documents :

D1: Grady R. et al. : "Axe-Txe, a broad-spectrum proteic toxin-antitoxin system specified by a multidrug-resistant, clinical isolate of *Enterococcus faecium*." Mol. Microbiol., vol. 47, no. 5, March 2003, pages 1419-1432

D2: Cherny I. et al. : "The YefM antitoxin defines a family of natively unfolded proteins." J. Biol. Chem., vol. 279, no. 9, 27 February 2004, pages 8252-8261

D3: Engelberg-Kulka H. et al. : "Bacterial programmed cell death systems as targets for antibiotics." Trends Microbiol., vol. 12, no. 2, February 2004, pages 66-71

2 - **Novelty** - Art. 33(1) and (2) PCT :

Document D1 discloses the identification of a toxin-antitoxin cassette on the pRUM plasmid of *Enterococcus faecium* which is homologous to YefM-yoeB present in the *Escherichia coli* chromosome (Abstract ; p. 1424, col. 1, last paragraph). Document D1 also provides a sequence alignment of the toxin-antitoxin families of proteins in a large range of bacteria including those disclosed in Table 1 and sequence listing of the present application (p. 1425, Figure 5).
The subject-matter of claims 29-30 can therefore not be considered as new in the light of document D1.

3 - **Inventive step** - Art. 33(1) and (3) PCT :

3.1 On the basis of the disclosure of document D1 (see above under Item V-2), it would be obvious to the person killed in the art to screen, with a very high expectation of success, molecules having the ability to prevent or disrupt the binding between toxin and corresponding antitoxin, when attempting to solve the problem of providing compounds able to induce bacterial cell death.
The subject-matter of claim 1 can therefore not be considered as involving an inventive step.

The same comment holds true for dependent claims 2-7 which relate to toxin-antitoxin pairs present in a series of bacteria which have already been disclosed in document D1 (p. 1425, Figure 5).

3.2 Claims 8-19 which relate to a method of treating an infection of bacteria by preventing or disrupting binding between a toxin and corresponding antitoxin produced in said bacteria cannot be regarded as involving an inventive step for the same reasons as those given above under Item V-3.1.
Moreover, the application does not provide any evidence of efficient treatment following the method of claims 8-19.

3.3 Given that the description does not contain any information indicating any

therapeutical effect of "pharmaceutical compositions" as defined in claims 20-28, it is not clear whether a technical problem is solved by the pharmaceutical compositions according to said claims which appear to result from a hypothetical theory with no support whatsoever.
Thus, the subject-matter of claims 20-28 cannot be considered as involving an inventive step.

3.4 The subject-matter of claims 31-33 consists in the selection of amino acid sequences from the sequence described in document D1. Such a selection can only be regarded as inventive, if the peptides present unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claims 31-33.

4 - **Industrial applicability** - Art. 33(1) and (4) PCT :

For the assessment of the present claims 8-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5 - **P-documents :**

Since the claim to priority of the present application (2 October 2003) appears to be valid, documents D2 and D3 that were published after the priority date, but before the filing date of the present application, are not relevant.

Re Item VII

Certain defects in the international application

Claim 13 appears to erroneously be dependent on claim 1 instead of claim 8 (Art. 5 PCT).

Re Item VIII

Certain observations on the international application

1. Claims 20-23 and 25-28 relate to an extremely large number of possible compounds. The claims contain so many possibilities, that a lack of clarity within the meaning of Art. 6 PCT arises to such an extend as to render a meaningful search and examination of the claimed scope impossible.
   Moreover, support within the meaning of Art. 6 PCT is to be found for only a very small proportion of the compounds claimed, *i.e.*, the peptides identified by SEQ ID NOs: 7-9. No disclosure within the meaning of Art. 5 PCT as regards any therapeutical effect can be found in the application.

2. The same comment holds true for the methods of treatment as defined in claims 8-19 (Art. 5 PCT and Art. 6 PCT).